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HPB

ORIGINAL ARTICLE

Prognostic value of the lymph node ratio after resection of periampullary carcinomas

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Abstract

Background: Data have indicated that the lymph node ratio (LNR) may be a better prognostic indicator than lymph node status in pancreatic cancer.

Objectives: To analyse the value of the LNR in patients undergoing resection for periampullary carcinomas.

Methods: A cut off value of 0.2 was assigned to the LNR in accordance with published studies. The impact of histopathological factors including a LNR was analysed using Kaplan–Meier and Cox regression methods.

Results: In total, 551 patients undergoing a resection (January 2000 to December 2010) were analysed. The median lymph node yield was 15, and 198 (34%) patients had a LNR > 0.2. In patients with a LNR of > 0.2, the median overall survival (OS) was 18 versus 33 months in patients with an LNR < 0.2 (P < 0.001). Univariate analysis demonstrated a LNR > 0.2, T and N stage, vascular or perineural invasion, grade and resection margin status to be significantly associated with OS. On multivariate analysis, only a LNR > 0.2, vascular or perineural invasion and margin positivity remained significant. In N1 disease, a LNR was able to distinguish survival in patients with a similar lymph node burden, and correlated with more aggressive tumour pathological variables.

Conclusion: A LNR > 0.2, and not lymph note status, is an independent prognostic factor for OS indicating the LNR should be utilized in outcome stratification.

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Introduction

Surgical resection remains the only potential curative treatment for periampullary cancers (ampulla, pancreatic head, distal common bile duct and duodenal); however, the 5-year survival has not improved significantly over the past decade and rarely exceeds 25%, with better results for ampullary lesions and worse outcomes for pancreatic head adenocarcinomas.[1,2] Several histopathological and tumour-related factors have been associated with a poor prognosis after surgery including tumour stage, size, grade, DNA content, resection margin and lymph node status.[3,4] The potential for more effective chemotherapeutic and biological agents may require modifications in traditional staging methods to facilitate effective patient selection for clinical trials, adjuvant therapies and for the purposes of prognosticatication.

An increasing number of reports are proposing the ratio between the number of lymph node metastases and the number of resected nodes, the so-called lymph node ratio (LNR), as a prognostic indicator of poor overall survival (OS), suggesting it may be more important than either LN status or the number of nodes evaluated alone in pancreatic cancer.[5–12] These studies and others in gastrointestinal cancers have shown that LNR either as a categorical variable using a cut-off of 0.2 (ranges 0.15–0.4) or as a continuous variable were strong negative prognostic factors.[13,14]

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The aim of this study was to analyse the LNR in patients undergoing a resection for periampullary carcinomas, assess its value as a prognostic factor on OS and evaluate its role in the context of other established prognostic factors.

Patients and methods

A total of 598 patients underwent a pancreatoduodenectomy at two high volume institutions; the Cleveland Clinic, Cleveland, Ohio, USA and St James University Hospital, Leeds, England between January 2000 and December 2010. Periampullary carcinomas comprised of tumours of the pancreatic head, ampulla complex and distal common bile duct. Duodenal carcinomas were excluded from this study.

In all patients, pre-operative radiological assessment included a thoracic, abdominal and pelvic computed tomography (CT), with magnetic resonance imaging of the pancreas and biliary tree performed when indicated. Operative techniques are similar at the two centres including the dissection of the pancreatic head and peri-pancreatic lymph nodes, and in the restoration of continuity of the gastrointestinal tract. A standard lymphadenectomy was performed in all patients. There were no differences in unit protocols directed decisions on the use of blood products with transfusion of red blood cells performed for those with haemoglobin <8 g/dl or symptomatic patients with haemoglobin of 8–10 g/dl.

For each patient, a demographic profile was collected together with details of histopathological features including resection margin status, vascular and perineural invasion. For all specimens, the total number of lymph nodes retrieved was recorded, as were the number with metastatic involvement. The American Joint Committee on Cancer (AJCC) TNM classification and the Royal College of Pathologist of United Kingdom have set 12 and 15 lymph nodes, respectively, as the minimal number to be collected at surgery and these figures were utilized to create categorical variables for the survival analysis.[15,16] For the purpose of this study, a positive resection margin was defined as the presence of a cancer cell within 1 mm of the transection margins.

The LNR was calculated by dividing the number of lymph nodes with metastasis present by the number of lymph nodes examined. For the main analysis, patients were divided into two groups according to a LNR either below or above 0.2. This was selected after review of the literature and utilized to maintain some uniformity when comparing with published studies. In addition, a further analysis was performed using different LNR cut-offs to evaluate the impact on OS and in patients with N1 disease.

Survival and follow-up

Peri-operative mortality was defined as death within 60 days after a resection and such patients were excluded from long-term survival analysis.[17] After initial post-operative review at 1 month, all patients were examined in the outpatient clinic at 3-monthly intervals for the first 2 years and annually thereafter. Overall survival was defined from the time of surgical resection to the date of death.

Data collection and statistical analysis

Student's *t*-test and Pearson's chi-squared test was used for continuous and categorical variables, respectively. Where variables did not follow a normal distribution, the Mann–Whitney *U*-test was applied. The Kaplan–Meier method was performed to analyse the overall survival. A multi-variate analysis was performed using Cox regression (Step-wise forward model) for variables reaching significance on univariate analysis that impacted upon OS. All statistical analyses were performed using the PASW for Windows™ version 18.0 (SPSS Inc, Chicago, IL, USA), and statistical significance was taken at the 5% level.

Results

During the study period, 598 patients underwent surgery for periampullary carcinomas. The complete datasets were not available for 5 (0.8%) patients, and together with peri-operative mortality of 42/593 (7%) the total number of patients available for the analysis of long-term survival was 551 (92.1%). Descriptive data for the entire cohort are shown in Table 1.

Long-term survival

The median follow-up was 32 months (range 0–130) and the median OS for the entire study cohort was 26 months (range 21–30). At the time of the analysis, 238 (40%) patients were still alive. Actuarial overall 1-, 3- and 5-year survival for the study group was 77% 39% and 27% respectively. Patient and tumour variables in the entire group of patients divided by the LNR < 0.2 and > 0.2 are shown in Table 2. The analysis of factors associated with OS is summarized in Table 3.

LNR, nodal status and OS

A LNR > 0.2 was an independent prognostic indicator of a poor outcome conferring an increased risk of death in the study population ($n = 551$) by 37% (HR 1.373, $P = 0.030$) Table 3. The median survival for patients with a NLR < 0.2 was 33 months compared with 18 months in patients with a LNR > 0.2 ($P < 0.001$) Fig. 1. In an attempt to make an observation on the impact of different LNR cut-offs on outcome, the median survival was assessed for incremental increases in LNR, and an inverse relationship between these factors was observed: > 0.05, > 0.1, > 0.15, > 0.2 and > 0.3 associated with 33, 20, 21, 18 and 18 months, respectively ($P <$ 0.001). The cut-off value for when LNR loses its value as an independent in a multivariate model was calculated as 0.08 (1.613 HR 1.076–2.419, $P = 0.021$, data not shown). A Kaplan–Meier curve for OS stratified by different LNR cut-off values (0.05, 0.1, 0.15, 0.2, 0.3) is shown in Fig. 2 and the 3-year actuarial survival was 42%, 36%, 27%, 23% and 22% for each cut-off respectively.

Table 1 Demographics, operative and histopathological data of entire cohort

Variable	
Age, years	
<65s	254 (43%)
>65	339 (57%)
Gender	
Female	261 (44%)
Male	332 (56%)
Pre-operative biliary stenting	
Yes	460 (78%)
No	133 (22%)
Tumour size (mm) mean (± SD)	28 ± 13
Tumour size	
<30	337 (57%)
>30	256 (43%)
Grade	
1	48 (8%)
2	268 (45%)
3	268 (45%)
4	7 (2%)
Tumour stage	
1	40 (8%)
2	129 (21%)
3	389 (67%)
4	35 (6%)
Node	
0	189 (32%)
1	404 (68%)
No of examined LN (median, IQR)	15 (8–21)
No of metastatic LN (median)	2
LNR	
Median	0.18
0–0.04	209 (35%)
0.05–0.09	74 (13%)
0.1–0.14	65 (11%)
0.15–0.199	47 (8%)
0.2–0.299	71 (12%)
>0.3	127 (21%)
Vascular invasion	
No	218 (37%)
Yes	375 (63%)
Perineural invasion	
No	174 (30%)
Yes	418 (70%)
Resection margin	
R0	466 (79%)
R1	127 (21%)

LNR, lymph node ratio; IQR, interquartile range.

Table 2 Variables associated with LNRs of <0.2 and ≥0.2 in the entire cohort

Variable	LNR <0.2	LNR ≥0.2	*P*
***N* (593)**	**394 (66%)**	**198 (34%)**	
Age, years			
<65	167 (42%)	87 (44%)	
≥65	227 (58%)	111 (56%)	0.79
Gender			
Female	179 (45%)	82 (41%)	
Male	215 (55%)	116 (59%)	0.353
Pre-operative biliary stenting			
No	109 (48%)	88 (44%)	
Yes	204 (52%)	110 (56%)	0.569
Tumour size, mm			
<30	245 (62%)	92 (46%)	
>30	149 (38%)	106 (54%)	<0.001
Grade			
1	37 (9%)	11 (5%)	
2	179 (45%)	88 (44%)	
3	169 (42%)	99 (51%)	
4	7 (4%)	0	0.06
Tumour stage			
1	30 (8%)	11(6%)	
2	101 (25%)	28 (14%)	
3	243 (61%)	144 (73%)	0.003
4	20 (6%)	15 (8%)	
No of examined LN (median, IQR)	15 (8–21)	16 (9–22)	0.569
No of examined LN			
<12	133 (34%)	58 (30%)	
>12	261 (66%)	140 (70%)	0.273
No of examined LN			
<15	190 (48%)	90 (45%)	
>15	204 (52%)	108 (55%)	0.523
No of metastatic LN			
0	191 (41%)	0	
1	92 (23%)	12 (6%)	
>2	111 (34%)	186 (94%)	<0.001
Vascular invasion			
No	170 (43%)	48 (24%)	
Yes	222 (57%)	153 (76%)	<0.001
Perineural invasion			
No	135 (35%)	39 (20%)	
Yes	259 (65%)	159 (80%)	<0.001
Resection margin			
R0	323 (81%)	143 (72%)	
R1	71 (19%)	55 (28%)	0.006

LN, lymph node.

Table 3 Overall survival after a resection: uni- and multivariate analysis

Covariant	*N* (551)	Univariate	*P*	Multivariate	*P*
		HR (95% CI)		HR (95% CI)	
Age, years					
<65	241				
≥65	310	1.295 (0.921–1.820)	0.137		
Gender					
Female	244				
Male	307	1.362 (0.970–1.914)	0.075		
Pre-operative stent					
No	12				
Yes	424	1.134 (0.760–1.691)	0.559		
Tumour size, mm					
<30	318				
>30	232	1.315 (0.933–1.855)	0.118		
Grade					
1	47				
2	251	2.005 (1.067–3.768)	0.031	2.172 (1.351–3.493)	0.001
3	243	1.804 (0.959–3.393)	0.061	3.400 (0.999–11.57)	0.051
4	7	1.012 (0.203–5.039)	0.981		
Tumour stage					
1	37				
2	124	1.476 (0.706–3.085)	0.31		
3	353	1.790 (0.906–3.536)	0.094		
4	31	0.850 (0.324–2.225)	0.740		
Node					
0	180				
1	371	2.046 (1.425–2.937)	<0.001	1.142 (0.092–13.874)	0.917
No of examined LN					
<12	182				
>12	369	1.165 (0.815–1.666)	0.403		
No of examined LN					
<15	258				
>15	293	0.832 (0.593–1.167)	0.287		
Involved LN					
No	183				
Yes	368	2.092 (1.459–2.999)	<0.001	1.246 (0.088–9.874)	0.457
No of metastatic LN					
0	183				
1	99	1.451 (0.886–2.374)	0.139		
>2	269	2.409 (1.638–3.534)	<0.001	2.146 (0.462–9.966)	0.330
LNR cut-off*					
<0.05	200				
>0.05	351	2.146 (1.507–3.057)	<0.001	1.205 (0.592–2.455)	0.607
<0.1	270				
>0.1	281	2.258 (1.600–3.187)	<0.001	1.435 (1.030–1.997)	0.033
<0.15	338				
>0.15	213	2.118 (1.479–3.031)	<0.001	1.311 (1.015–1.746)	0.039

Table 3 *Continued*

Covariant	*N* (551)	Univariate	*P*	Multivariate	*P*
		HR (95% CI)		HR (95% CI)	
<0.2	371				
>0.2	180	2.253 (1.453–3.297)	<0.001	1.373 (1.016–1.854)	0.030
<0.3	432				
>0.3	118	2.190 (1.409–3.404)	<0.001	1.352 (1.031–1.773)	0.029
Vascular invasion					
No	176				
Yes	375	1.625 (1.161–2.274)	0.005	1.322 (1.024–1.707)	0.032
Perineural invasion					
No	167				
Yes	384	2.280 (1.809–4.648)	<0.001	1.894 (1.430–2.514)	0.001
Resection margin					
R0	438				
R1	113	2.900 (1.809–4.645)	<0.001	1.457 (1.129–1.880)	0.004

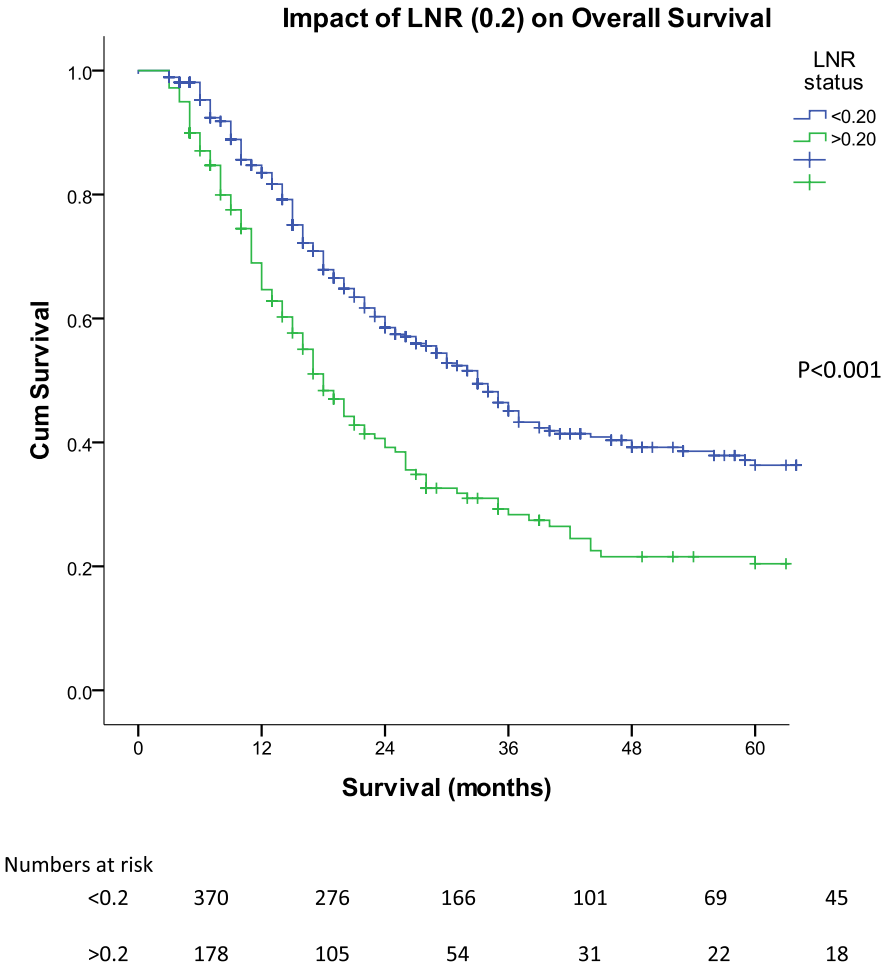
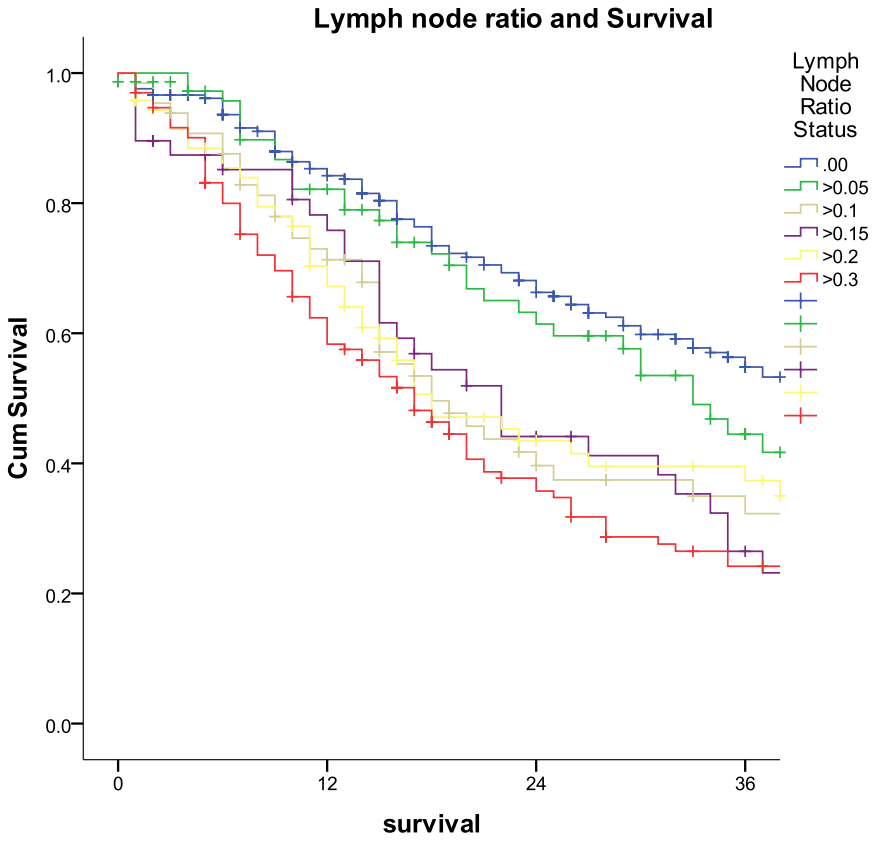


Figure 1 The impact of the lymph node ratio (LNR) 0.2 on overall survival (OS), $P < 0.001$



Numbers at risk

0	199	159	104	76
0.05-0.09	67	49	32	16
0.1-0.14	68	46	21	11
0.15-0.19	31	25	12	5
0.2-0.3	61	39	21	15
>0.3	118	70	33	15

Figure 2 Overall survival (OS) stratified according to different lymph node ratio (LNR) cut-off values

The median number of lymph nodes evaluated in the overall group was 15 (Table 1). There was no significant change in the median LN yield over the time period; 14 (2000–2005) versus 16 (2005–2010), $P = 0.120$. When examined as a continuous LN number or categorical variable (either 12 or 15) it was not associated with OS on univariate analysis (Table 3). Patients with N1 disease ($n = 370$) had a shorter median OS: 21 months compared with 48 months $P < 0.001$ in N0 ($n = 181$) disease. Furthermore, the number of positive lymph nodes was associated with a corresponding decrease in OS: N0 = 48 months; 1 positive LN = 30 months ($P = 0.038$); and ≥2 lymph nodes = 20 months ($P < 0.001$). While LN positive status was significant at a univariate level (HR 2.092 (1.638–3.534), $P < 0.001$) its inclusion in a multivariate model failed to reach statistical significance (Table 3).

To investigate the effect of the number of lymph nodes retrieved on survival in either N0 or N1 disease groups were divided into either </≥12 or </≥15 nodes. In N0 disease, there was a non-significant trend towards a poorer outcome in terms of long-term survival in patients who had less than 12 nodes retrieved (41 months versus 56 months; $P = 0.26$). There was no significant difference in long-term outcome in N1 disease if less than 12 nodes were evaluated (19 months versus 22 months; $P = 0.917$). When the analysis was repeated with the LN retrieval cut-off set at 15 there was no difference in outcome for either N0 or N1 disease.

In a subset analysis of N1 ($n = 370$) disease, the factors shown to be significant at a univariate level included: grade > 2, > 2 lymph nodes positive, LNR ≥0.2, a positive resection margin, and vascular and perineural invasion. Furthermore, all these variables were shown to be independent prognostic factors impacting on OS in a multivariate model: grade > 2 [HR 1.688 (1.055–2.700), $P = 0.029$], LNR ≥0.2 [HR 1.317 (1.020-1.859) $P = 0.037$], positive resection margin [HR 1.456 (1.128–1.878), $P = 0.004$], vascular invasion [HR 1.307 (1.009–2.001), $P = 0.021$] and perineural inva-

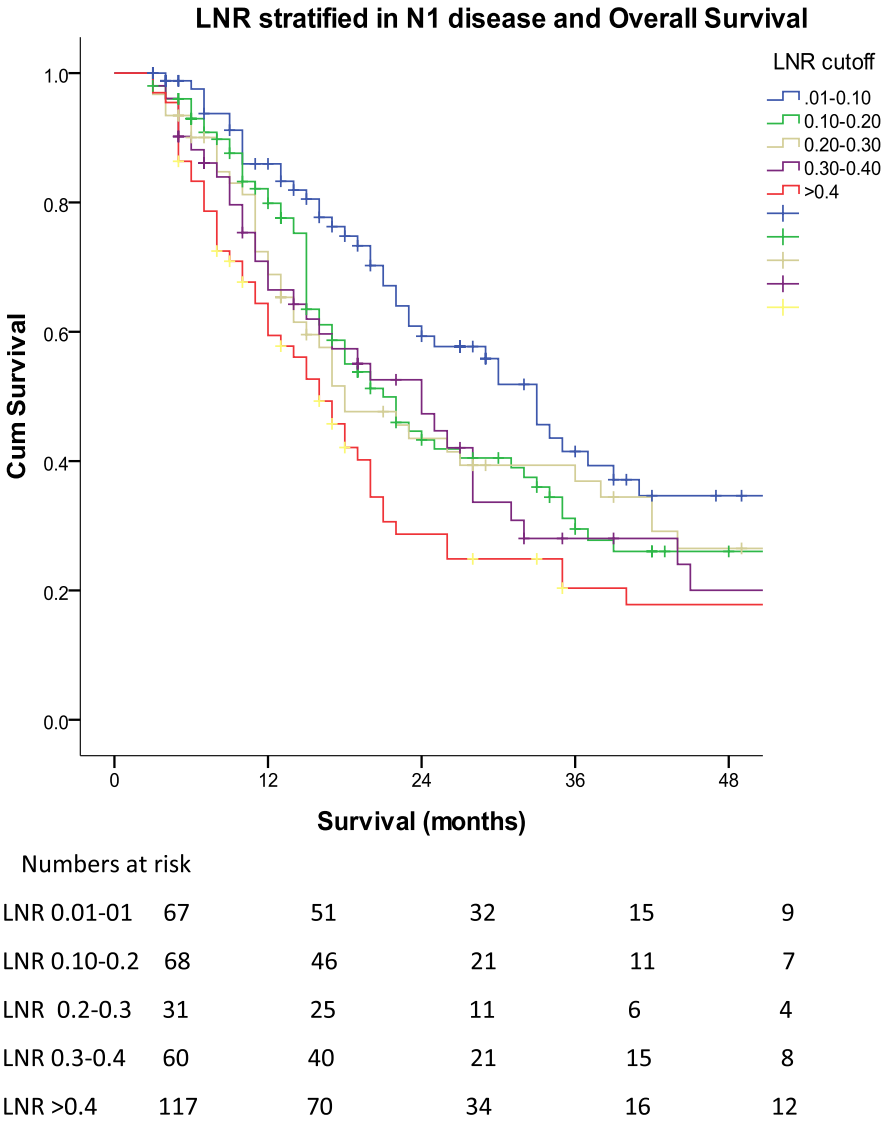


Figure 3 Overall survival (OS) stratified according to different lymph node ratio (LNR) cut-off values in N1 disease

sion [HR 1.895 (1.430–2.511), $P < 0.001$]. When the LNR cut-off was replaced by (0.1–0.2), (0.2–0.3), (0.3–0.4) or > 0.4, the LNR remained an independent prognostic factor in N1 disease.

In evaluating the role of LNR in N1 disease specifically, there was an observed trend demonstrating poorer OS as the LNR increased from (0.1–0.2), (0.2–0.3), (0.3–0.4) or > 0.4 and was associated with median survivals of 21, 18, 16 and 16 months, respectively (Fig. 3). Furthermore, an increasing LNR was shown to be able to differentiate long-term survival in patients with similar LN involvement (Table 4) and progressive tumour features (Table 5).

Table 4 The median survival stratified by lymph node ratio (LNR) cut-off values in N1 disease involving a similar lymph node burden

	N	LNR (0.01–0.2) months	LNR (0.2–0.4) months	LNR >0.4 months	*P*
LN +ve 0–3	210	24	18	16	0.730
LN +ve 4–5	72	27	25	13	0.0201
LN +ve >6	85	16	15	12	0.052

LN +ve = lymph node positivity.

Discussion

This study has confirmed that a LNR (> 0.2), together with vascular or perineural invasion, and a positive resection margin are all independent prognostic factors in determining long-term survival in patients undergoing resection for periampullary tumours. Additionally, results have demonstrated a progressively poor outcome in terms of both the overall cohort, and specifically in N1 disease, as the LNR increases from 0.1 to > 0.3.

Table 5 Variation in tumour features as the lymph node ratio (LNR) increases

	LNR (0.01–0.2) (%)	LNR (0.2–0.4) (%)	LNR >0.4 (%)	*P*
Resection margin +ve	17	20	35	0.012
Vascular invasion	32	41	52	0.051
Perineural invasion	69	75	83	0.035
Size >30 mm	48	52	55	0.599
Grade				
1	6	4	8	0.575
2	44	46	44	
3	47	50	48	
4	3	0	0	

The presence of nodal disease represents a poor prognostic factor,[18] is associated with relatively high rates of LN metastasis to para-aortic nodal stations in periampullary tumours[19,20] and, in the current study, has been shown to confer poorer OS than N0 disease. Results confirm House *et al.*'s observation that as the number of involved LN increases ≥2 there is an associated reduction in OS.[21] Importantly, however, in spite of the presence of nodal disease, or more specifically ≥2 nodes involved being associated with poor OS on a univariate level, it failed as an independent prognostic factor in a multivariate model herein and concurs with previous studies.[7,10,22]

Several authors have previously advocated performing an extended lymphadenectomy to improve lymphatic clearance and the potential prognosis.[23,24] A number of systematic reviews, randomized controlled trials and meta-analyses including a recent study describing 16 studies containing 1909 patients refute this approach and show no survival advantage associated with an extended pancreatoduodenectomy compared with a standard lymphadenectomy.[25,26] Furthermore, given the predicted small difference in outcome, the number of patients required to show a statistically significant difference between a standard and extended lymphadenectomy would be so large that such an adequately powered randomized controlled trial would be unfeasible.[27]

Pawlik *et al.* demonstrated that less than 12 nodes retrieved in N0 disease resulted in poorer OS and Tomlinson and colleagues highlighted that ≥15 nodes were required to confer a survival advantage in N0 disease.[9,28] The number of lymph nodes required to minimize the risk of the stage migration phenomenon is proposed to be between 10 and 15.[29,30] In this study, the impact of achieving a LN yield of both the American Joint Committee on Cancer (AJCC) TNM classification and the Royal College of Pathologist of United Kingdom criteria which are 12 and 15, respectively, is reported.[15,16] While there was an observed trend towards poorer OS in N0 disease with < 12 nodes retrieved there was no statistical significance in OS when either >15 nodes in N0 or >12 & >15 nodes obtained in N1 disease. Furthermore, the analysis of the number of lymph nodes as a categorical value of 12 or 15 (or indeed as a continuous variable, data not shown) failed to show any correlation in a univariate analysis.

Several investigators have attempted to explore the relevance of not only the number of examined LN but also the utility of the LNR in various gastrointestinal cancers including oesophageal, gastric, colorectal and pancreatic carcinoma.[31] By definition, this marker incorporates both the extent of the metastatic disease (number of positive LN), the quality of a lymphadenectomy and the provision of an adequate specimen for the pathologist (the number of LN retrieved). In stage 3 colorectal cancer, the LNR provides a superior and independent prognostic stratification compared with the assessment of the number of positive nodes.[31] In pancreatic cancer, there have been a number of studies (predominantly incorporating case series of around 50–100 patients) that have reported the negative impact of an LNR range of between 0.10–0.40 on long-term outcomes.[6–8,10,11,22,32–35] The current study includes more than 500 patients and it follows only three others with larger numbers.[9,12,21]

No consensus has been established for the most prognostically accurate cut-off of LNR but in a review of the literature it appears to centre around 0.2 and its variance probably is a reflection of multiple components including tumour biology, an adequate lymphadenectomy and pathological examination the specimen to achieve maximum LN yield. House *et al.* in their study of 906 patients analysed LNR as a continuous variable and determined a cut-off value of 0.18 in predicting outcome.[21] The median survival of patients with an NLR < 0.2 in the current study was 33 months which was significantly greater than the 18 months in those with an LNR of >0.2 and results demonstrate a decrease in OS as LNR increases. Furthermore, in keeping with the findings of both Pawlik *et al.* and Bhatti *et al.*, the current data demonstrated that the LNR is a valid marker for predicting adverse tumour factors such as vascular and perineural invasion and a positive resection margin.[7,9]

Tissue processing and meticulous pathological assessment are now becoming part of robust protocols in establishing true resection margin status and challenging marked variability in LN counts in tissue.[36–38] The technique now being adopted globally for the histological assessment of pancreatic specimens was developed in Leeds and introduced into practice in the Cleveland Clinic in 2009.[39] While all the Leeds specimens were processed using the new technique, it was only in the later period of the study was it used in both centres and to remove this as a confounding factor, the definition of positive margins was that traditionally utilized namely the presence of a tumour at the surgical resection margins rather than the new concept which also addresses in detail non-surgical resection margins. As there is no difference in the surgical treatment of the specimen, it was not felt that this would influence LN harvest and hence the LNR. Indeed this has been confirmed by Liska *et al.*[38] Another factor clearly evident when the new method of tissue sectioning is applied is a change in the origin of the

periampullary tumours. The data from Leeds would suggest that with the new technique of histopathological examination, which allows a more accurate assessment of the periampullary region, the proportion of pancreatic, ampullary and ductal carcinomas is close to equal, whereas traditional methods of tissue preparation would suggest a predominance of pancreatic head lesions. Consequently to avoid an inaccurate representation, periampullary carcinomas are not categorized individually and included in a multivariate analysis in this study. This is in difference to previous studies and acknowledges that some would consider this as a limitation.

There are in addition other limitations of the study. It is difficult to accurately account for surgical decision-making in performing more extensive LN dissections between different surgeons/centres in specific patients and not others. However, the finding that neither the number of lymph nodes retrieved or the proportion with >12 nodes harvested has not altered over time would lead us to assume that the technique has not significantly changed in the study period. It could be argued that the observation of a poorer OS in N0 disease where less than 12 nodes were retrieved could have represented missing nodes but as there was no correlation between the number of LN examined and outcome in the statistical model, it would appear that under-staging does not account for this, or if it is involved its influence is weak. The role of adjuvant chemotherapy has not been studied in this study as there was significant variation in its use across the 10 years of the study in relation to whether it was offered or not, and the constituents of the treatment.

The study is retrospective and hence there are questions as to data interpretation in particular in relation to some of the finer aspects of pathological assessment as at the commencement of the study there was no sub-specialization in pancreatic histopathology. However, in spite of this, the increasing number of retrospective studies that now exist in this subject area means that there is now the need for prospective studies in collaboration with potential adjuvant treatments to provide the next level of evidence in establishing the most optimal cut off value for LNR, utility as a negative prognostic factor and deciding on treatment algorithms.[32]

Conclusions

A LN ratio > 0.2 (and not LN status or LN yield) is, together with neurovascular invasion, and resection margin an important independent prognostic factors for OS in periampullary carcinomas. These data, in a large series, confirms previous studies in leading to the proposal of its utilization in outcome stratification. Prospective studies are now required to determine whether the LNR can be used to predict the need for, and benefit from chemotherapy.

Conflicts of interest

None declared.

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